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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,294	DOW ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Pursuant to the interview dated September 10, 2008, and in view of Applicants' claim amendments, the finality of the rejection of the Office action dated March 19, 2008 has been withdrawn. Applicants' after-final amendment and response dated February 19, 2009, to the Office action dated March 19, 2008, have been entered. Claims 1 and 13 have been amended and claims 11 and 12 cancelled. No claims were newly added. Accordingly, claims 1-10 and 13-22 are pending in the application and are currently under examination.

As an initial matter, Applicants should note that base claims 1 and 13 have been amended to delete the elected species of an oligonucleotide containing no CpG motifs, elected without traverse in the response dated November 10, 2006, and replaced with the generic DNA molecule, when no such generic claim was previously presented. The amendment has thereby improperly broadened the claims. The species restriction stands and is applicable to the instant claims.

Response & Maintained Claim Rejections - 35 USC § 112 – Written Description

Claims 1-22 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, Applicants' cancellation of claims 11 and 12 renders their rejections moot. The rejection set forth on pp. 2-5 of the previous office action dated March 19, 2008 is maintained for claims 1-10 and 13-22, for reasons of record. Applicants' amendment of the claims to limit the composition to a DNA molecule containing no CpG motifs and from more than 25 to about 100 nucleotides in length, in part addresses the ground for rejection, while introducing new issues as outlined below.

Applicants argue that in light of the Examiner discussions and amendments made based on the Examiner interview the rejections are rendered moot. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it is noted that Applicants' claim amendments have adequately addressed issues with regard to oligonucleotide length. However, the instant claims embrace a genus of

DNA molecules lacking CpG motifs, that include double-stranded DNAs that would further be able to elicit a therapeutic systemic, non-antigen-specific immune response. The specification is however silent on such DNA structures having the ability to generate a therapeutic non-antigen specific immune response as claimed. Applicants' assertion that support for the amendment is found in paragraphs [0131-0137], is incorrect, because the cited paragraphs are relevant to cDNA molecules encoding antigens, and paragraph [0178] further encompasses plasmids encoding genes, that are not commensurate with the non-CpG oligodeoxynucleotides of between 25 and 100 nucleotides in length.

Thus, the rejection is maintained for claims 1-10 and 13-22, for reasons of record, and the foregoing discussion. An amendment of base claims 1 and 13 replacing "DNA molecule" with "oligodeoxynucleotide" would obviate the rejection.

Response & Maintained Claim Rejections - 35 USC § 112 - Scope of Enablement

Claims 1-22 stand rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicants' cancellation of claims 11 and 12 renders their rejections moot. The rejection set forth on pp. 4-8 of the office action dated June 15, 2007, and pp. 5-8 of the previous office action dated March 19, 2008 is maintained in modified form, for reasons of record. Applicants' amendment of the claims to limit the composition to a DNA molecule containing no CpG motifs and from more than 25 to about 100 nucleotides in length, in part addresses the ground for rejection. In view of Applicants' claim amendments and upon further consideration the rejection has been modified to indicate an enabled scope for the invention, wherein the specification is enabled for a composition for the elicitation of a systemic, non-antigen specific immune response in a mammal comprising: a. a liposome delivery vehicle; and b. an oligodeoxynucleotide containing no CpG motifs and from more than 25 to about 100 nucleotides in length; wherein said composition elicits a systemic, non antigen specific Thl immune response in said mammal; and a method comprising administering to a mammal an amount of said composition effective to elicit a Th1 immune response, does not reasonably provide an enablement for said method or composition as a therapeutic, or wherein the non-CpG motifs are present in any DNA molecule, as broadly claimed. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants state that the §112, first paragraph rejections were discussed in the Examiner Interview and the amendments render the rejections moot. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it is noted that Applicants' claim amendments have adequately addressed issues with regard to oligonucleotide length. However, the instant claims embrace a genus of DNA molecules lacking CpG motifs, that include double-stranded DNAs that would further be able to elicit a therapeutic systemic, non-antigen-specific immune response. Further, the Examiner did not indicate that the language of therapeutic for the claimed composition remained acceptable.

As previously indicated, the claims have been examined in view of the as filed specification, and embrace a method for using a composition comprising a liposome delivery vehicle and an oligonucleotide containing no CpG motifs composition in a treatment of tumors in a mammal when administered as a therapeutic vaccine. The specification states: "The above-mentioned method and compositions of the present invention have the advantages of eliciting a systemic, non-antigen specific immune response in a mammal, and more particularly, of eliciting a systemic, anti-viral immune response in a mammal. Additionally, the method and composition of the present invention can elicit a systemic, anti-tumor immune response in a mammal. Such an anti-tumor immune response can result in the reduction of a tumor in the mammal." (paragraph [0015], p. 4).

The previous office action set forth detailed observations regarding the deficiencies in Examples 12-15 that included the delivery of the combination therapeutic composition. For instance, Example 12 describes the i.v. injection of oligodeoxynucleotides lacking CpG motifs, ranging in size from 10 to 100 nucleotides into mice. The results are presented in Figure 30 and showed that while some activation of $CD8^+/CD69^+$ cells was detectable for oligodeoxynucleotides of 25 and longer lengths, the response was inferior in all cases, compared to a control 20 mer containing two CpG motifs, and contrary to the statement in paragraph [00228] of the instant specification, the responses were not as great as that elicited by the CpG

containing oligonucleotide. Further, not only is there no apparent correlation between oligodeoxynucleotide size and CD69 activation (as evidenced by a decrease in activation in the 75 mer and 100 mer oligos from that seen with a 50mer), no 20 mer was included in the group of oligodeoxynucleotides lacking CpG to correspond to the size of control oligodeoxynucleotide.

Example 14 describes the i.v. injection into mice of oligodeoxynucleotides lacking CpG motifs, wherein the oligodeoxynucleotides were either a 10mer or a mixture of 50mer and 75 mer, followed by the isolation and culture of spleen cells for measuring IFNγ release. Here, the results from the 100 mer oligonucleotide were omitted, and IFNγ release was only detectable for the mixture of 50mer and 75 mer. As the positive controls in the experiment included plasmid DNA, it is not clear what conclusions may be derived by such non-analogous comparisons. It is noted that the 20mer control oligodeoxynucleotide containing two CpG sequences, yielded very little measurable IFNγ release.

Example 15 describes the results obtained from an experiment similar to that noted in Example 14, except that IFN-α release was measured. Again, only the mixture of 50mer and 75 mer oligodeoxynucleotides resulted in an increase in IFN-α production over that observed with the CpG oligonucleotide. However, as the oligodeoxynucleotides are of different lengths and sequences, no definitive conclusions can be drawn from the experiment. It is further noted that the results from Examples 14 and 15, depicted in Figures 32 and 33 are not directly relevant to the instant claims, as the claims are not directed to a mixture two different oligodeoxynucleotides, but rather a single oligonucleotide. Applicants have also failed to respond to the deficiencies in Example 15. Moreover, none of the examples using oligodeoxynucleotides lacking CpG motifs, included the assessment or evaluation of tumors correlate the immune responses generated with any therapeutic effect on any disease or infection. The specification is further silent on the sequence specific effects of the oligos, or the minimum size of an oligonucleotide required to elicit a cytokine response, or whether the cytokine release measured for some of the CpG deficient oligodeoxynucleotides would constitute a therapeutically effective amount in the treatment of any disease or infection. The previous office action therefore highlighted the deficiencies in the Examples, and as such analysis is in accord with the *Wands* factors, that include the working examples and the amount of direction or

guidance presented, the Examples fail to support an enablement for the claimed composition as a therapeutic.

It is further noted that the working examples employed oligodeoxynucleotides, and not DNA molecules of any structure, that include double stranded DNA. Therefore, a person of skill in the art would therefore have to engage in additional undue experimentation to develop a composition comprising any liposome and any DNA of any sequence composition that when administered to a mammal, would have a therapeutic effect.

Thus, the rejection is maintained for claims 1-10 and 13-22 for reasons of record, and the foregoing commentary.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 10, 13-19, and 22 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Auf et al. (Clin. Cancer Res. 7:3540-3543; 2001), in view of Vollmer et al. (Antisense & Nucl. Acid Drug Dev. 12:165-175; 2002), and further in view of Tam et al. (U.S. Patent Publication No.: 2004/0009944; effective filing date May 10, 2002).

The claims embrace a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide from more than 25 to about 100 nucleotides in length containing no CpG motifs, having the ability to elicit a systemic non-antigen specific Th1 immune response in a mammal, and a method comprising administering said composition to a mammal.

It is noted that base claim 1 is directed to a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Auf et al. describe phosphorothioate oligodeoxynucleotides containing CpG motifs that display immunostimulating activity without antigen, in rats and mice, inducing tumor rejections through an early activation of innate immunity and priming of a specific immune response against glioma cells (Title and Abstract). Auf et al. further describe a 22mer oligodeoxynucleotide in which the CpG motifs have been mutated (second column, p. 3540), that when administered to rats, resulted in a lesser reduction in tumor volume than a corresponding oligodeoxynucleotide containing two CpG motifs (Fig. 1, p. 3541).

While the oligodeoxynucleotide described by Auf et al. having no CpG motifs was not greater than 25 nucleotides in length, and was not administered with a liposome delivery vehicle, such were known in the prior art.

Vollmer et al. describe highly immunostimulatory CpG-free oligodeoxynucleotides for activation of human leukocytes, having length-dependent immunostimulatory effects, and less efficient in stimulating human immune cells (Title and Abstract). Vollmer et al. specifically describe CpG-free oligodeoxynucleotides having 27 and 30 nucleotides in length, in Table 1, p. 166, thus curing the deficiency in Auf et al. for oligodeoxynucleotide length.

Tam et al. describe immunostimulatory oligonucleotides bearing methylated CpG dinucleotide motifs encapsulated in a lipid particle for *in vivo* use (Title and Abstract). The lipid particle is further described as a liposomal particle comprising a cationic lipid selected from a group of cationic lipids consisting of DDAB, DODAC, DOTAP, DMRIE, DOSPA, DMDMA, DC-Chol, DODMA DODAP (paragraph [0016], and DOTMA (paragraph [0098], and wherein the lipid particle preferably comprises cholesterol (paragraphs [0406] and [0119]). Extruded lipids are described in paragraph [0123], and the liposomes are further disclosed as preferably multilamellar (paragraph [0078]). The lipid-nucleic acid formulation further comprises a

pharmaceutically acceptable carrier, buffer or diluent (paragraph [0014]). With regard to the nucleic acid to lipid ratios, Tam et al. state that dosages of lipid-nucleic acid formulations depend on the desired drug:lipid ratio of the composition, and one skilled in the art can select proper dosages based on the information provided (paragraph [0172]). Applicants should further note that as indicated in MPEP 2144.05: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Routine optimization is not inventive, and no evidence has been presented here to suggest that the selection of the claimed nucleic acid to lipid rations was other than routine or that the results should be considered unexpected. The non-criticality of the concentration ratio is evidenced by the wide range claimed.

The compositions and methods described by Auf et al., Vollmer et al. and Tam et al. are directed to the delivery of oligodeoxynucleotides to elicit an immune response. Thus a person of ordinary skill in the art would have been motivated to combine their respective teachings to elicit a systemic non-antigen specific immune response in a mammal.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of non-CpG containing oligodeoxynucleotides and liposome delivery particles, resulting in the composition and method of the instantly claimed invention, with a reasonable expectation of success. It should be noted that the ability of the composition to elicit a Th1 immune response in a mammal is a property inherent to the composition.

As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim. See, e.g., *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed.Cir. 1997).

Claims 1, 7-9, 13 and 19-21 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Auf et al. (Clin. Cancer Res. 7:3540-3543; 2001), in view of Vollmer et al. (Antisense & Nucl. Acid Drug Dev. 12:165-175; 2002), and Tam et al. (U.S. Patent Publication No.: 2004/0009944; effective filing date May 10, 2002), as applied to claims 1-7, 10, 13-19, and 22 above, and further in view of Klinman et al. (U.S. Patent Publication No.: 2003/0060440; filed Feb. 6, 2002).

The claims encompass embrace a composition comprising a liposome delivery vehicle and an oligodeoxynucleotide from more than 25 to about 100 nucleotides in length containing no CpG motifs, comprising dextrose in water as an excipient, having the ability to elicit a systemic non-antigen specific Th1 immune response in a mammal, and a method comprising administering said composition to a mammal. The specification exemplifies dextrose in water as a non-ionic diluent.

Auf et al. describe phosphorothioate oligodeoxynucleotides containing CpG motifs that display immunostimulating activity without antigen, in rats and mice, inducing tumor rejections through an early activation of innate immunity and priming of a specific immune response against glioma cells (Title and Abstract). Auf et al. further describe a 22mer oligodeoxynucleotide in which the CpG motifs have been mutated (second column, p. 3540), that when administered to rats, resulted in a lesser reduction in tumor volume than a corresponding oligodeoxynucleotide containing two CpG motifs (Fig. 1, p. 3541).

Vollmer et al. describe highly immunostimulatory CpG-free oligodeoxynucleotides having 27 and 30 nucleotides in length, in Table 1, p. 166.

Tam et al. describe immunostimulatory oligonucleotides bearing methylated CpG dinucleotide motifs encapsulated in a lipid particle for *in vivo* use (Title and Abstract). The lipid-nucleic acid formulation further comprises a pharmaceutically acceptable carrier, buffer or diluent (paragraph [0014]).

While the pharmaceutical diluent composition described by Tam et al. did not comprise dextrose, such were known in the prior art.

Klinman et al. describe oligodeoxynucleotides comprising a CpG motif for inducing an immune response (Abstract), formulated in a pharmaceutically acceptable fluid such as water, that include aqueous dextrose (paragraph [0092]). As indicated above, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

The compositions and methods described by Tam et al. and Klinman et al. are directed to the delivery of oligodeoxynucleotides to elicit an immune response. Thus a person of ordinary skill in the art would have been motivated to combine their respective teachings to elicit a systemic non-antigen specific immune response in a mammal.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize aqueous dextrose in a pharmaceutical formation of oligodeoxynucleotides and liposome delivery particles, resulting in the composition and method of the instantly claimed invention, with a reasonable expectation of success.

Conclusion

Claims 1-10 and 13-22 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633